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Debuf, Marie Julie; Benoit, Valérie; Cassart, Marie; Gajewska, Kalina; Gauquier, Nathalie; Meunier, Colombine; Rassart, Anne; Maystadt, Isabelle

*Published in:*  
Clinical Case Reports

*DOI:*  
[10.1002/ccr3.2228](https://doi.org/10.1002/ccr3.2228)

*Publication date:*  
2019

*Document Version*  
Publisher's PDF, also known as Version of record

#### [Link to publication](#)

*Citation for published version (HARVARD):*

Debuf, MJ, Benoit, V, Cassart, M, Gajewska, K, Gauquier, N, Meunier, C, Rassart, A & Maystadt, I 2019, 'Agenesis of olfactory bulbs: A forgotten diagnostic indicator of acampomelic campomelic dysplasia', *Clinical Case Reports*, vol. 7, no. 7, pp. 1352-1354. <https://doi.org/10.1002/ccr3.2228>

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# Agenesis of olfactory bulbs: A forgotten diagnostic indicator of acampomelic campomelic dysplasia

Marie-Julie Debuf<sup>1,2</sup> | Valérie Benoit<sup>1</sup> | Marie Cassart<sup>3</sup> | Kalina Gajewska<sup>4</sup> |  
Nathalie Gauquier<sup>5</sup> | Colombine Meunier<sup>1</sup> | Anne Rassart<sup>6</sup> | Isabelle Maystadt<sup>1,7</sup> 

<sup>1</sup>Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium

<sup>2</sup>Service de Pédiatrie, Université Catholique de Louvain, Brussels, Belgium

<sup>3</sup>Services de Radiologie et Médecine Foetale, Hôpitaux Iris Sud et CHU St Pierre, Brussels, Belgium

<sup>4</sup>Service de Gynécologie et d'Obstétrique, Hôpital Civil Marie Curie, Charleroi, Belgium

<sup>5</sup>Service de Radiologie, Hôpital Civil Marie Curie, Charleroi, Belgium

<sup>6</sup>Service de Néonatalogie, Hôpital Civil Marie Curie, Charleroi, Belgium

<sup>7</sup>Département de Médecine, URPHYM, Université de Namur, Namur, Belgium

## Correspondence

Isabelle Maystadt, Centre de Génétique Humaine, Institut de Pathologie et de Génétique, Gosselies, Belgium.  
Email: isabelle.maystadt@ipg.be

## Abstract

Campomelic dysplasia (CD) and its variant acampomelic campomelic dysplasia (ACD) are caused by *SOX9* haploinsufficiency. This gene encodes a transcription factor crucial for embryogenesis and primarily expressed in the olfactory bulbs. The detection of agenesis of olfactory bulbs could help establish a prenatal diagnosis of CD or ACD, although prevalence of this sign remains unknown.

## KEYWORDS

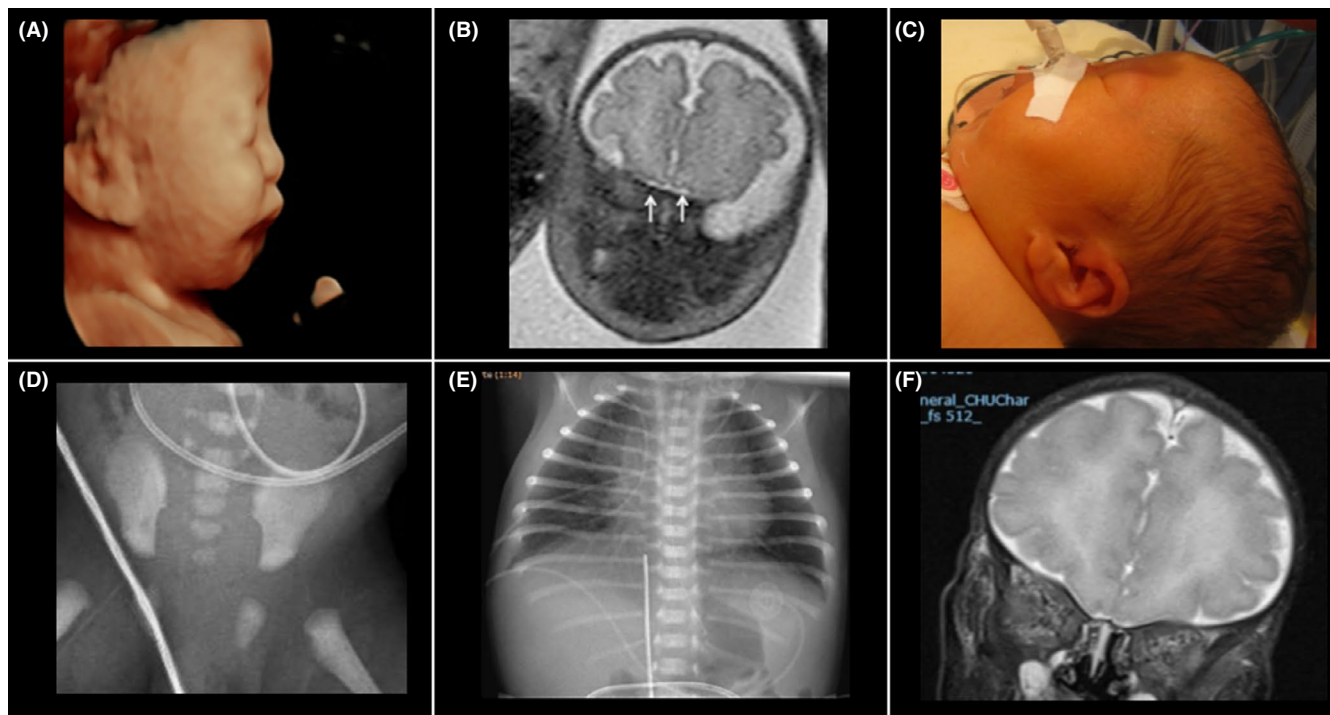
acampomelic campomelic dysplasia, olfactory bulbs agenesis, prenatal diagnosis, *SOX9* gene

## 1 | INTRODUCTION

Campomelic dysplasia (CD) is a rare developmental condition caused by heterozygous mutations in the *SOX9* gene. The most common features of CD are short and bowed long bones, narrow iliac wings, dislocated hips, pelvic malformations, 11 pairs of ribs, club feet, cleft palate, microretrognathia, low-set ears, a flat face, and relative macrocephaly. Patients with a 46,XY karyotype usually have ambiguous genitalia. Late polyhydramnios, a short corpus callosum, and diminished white matter have also been reported.<sup>1,2</sup> Curvature of the limbs is not always

present, representing a clinical variant of CD named acampomelic campomelic dysplasia (ACD), which has also been defined.<sup>3</sup> Respiratory compromise due to a narrow thorax and tracheobronchomalacia is responsible for early neonatal death.

The clinical severity and high neonatal lethality of CD emphasize the importance of accurate prenatal diagnosis of this condition. Currently, more and more efficient ultrasonographic (US) examination and magnetic resonance imaging (MRI) are being used to help obstetricians detect early signs of skeletal dysplasia. Nevertheless, it remains a challenge to differentiate between these skeletal disorders.



**FIGURE 1** Pre- and post-natal images illustrating the morphological features of the patient. A, Ultrasound performed at 33 wk and 6 d gestation (fetal profile) showing retrognathia, a flat face, low-set ears and midfacial hypoplasia. B, Prenatal magnetic resonance imaging (MRI) demonstrated the absence of olfactory bulbs and sulci. C, Neonatal clinical exam revealed a flat face, prominent eyes, low-set ears, a short nose, retrognathia and a short and thick neck. D, X-rays showed narrow hypoplastic iliac wings, dislocated hips, the verticalization of the ischia and a lack of pubis ossification. E, Chest X-rays showed 12 pairs of gracile ribs that are hair. F, Postmortem cerebral MRI showed a global simplified gyral pattern and the absence of olfactory bulbs

## 2 | CASE REPORT

Here, we report on a female neonate born at term by vaginal delivery from nonconsanguineous Caucasian parents. The father was 31 years old, and the 23-year-old mother was primigravida. She has not been in contact with mutagens during pregnancy. The pregnancy was marked by the detection of a polymalformative syndrome associated with polyhydramnios. Prenatal US examination revealed a Pierre Robin sequence (cleft palate, glossoptosis, retrognathia), a flat face, low-set ears, and club feet (Figure 1A). The limbs were not curved. Repeat amniocenteses were carried out in response to polyhydramnios to drain the excess fluid, and comparative genomic hybridization (CGH) arrays performed on the amniotic fluid showed a normal female karyotype (46,XX). A prenatal MRI scan revealed the absence of olfactory bulbs and tracts, a short corpus callosum and a hypoplastic cochlea (Figure 1B). At birth, the newborn weighed 2.690 kg (P37 on the Fenton growth chart), measuring 46 cm in length (P27) with a head circumference of 35 cm (P92). The Apgar score was five after 1 minutes and seven after 5 and 10 minutes. The newborn immediately presented with respiratory distress, and required continuous positive airway pressure. Upon clinical

examination, we noted facial dysmorphism with a flat face, prominent eyes, low-set ears, a short nose, and a cleft palate (Figure 1C). The neck was short, the upper limbs were stiff with elbow contracture, and the hands were short and large. The lower limbs were not curved, but the feet showed equinus deformity. The external genitalia were female and normal. The esophagus was permeable, and there was no hepatosplenomegaly. A cardiac US showed no malformation. On day 5, the patient presented with respiratory failure which required invasive ventilation after intubation. Chest and abdominal radiographs showed narrow, hypoplastic iliac wings, dislocated hips, the verticalization of the ischia, and a lack of ossification of the pubis (Figure 1D). There were 12 pairs of ribs, but they were gracile (Figure 1E). On day 8, the patient died from cardiorespiratory failure. The parents refused an autopsy. A postmortem cerebral MRI showed a global simplified gyral pattern and confirmed agenesis of the olfactory bulbs and short corpus callosum (Figure 1F). A CGH array was performed on a blood sample, which confirmed the absence of chromosomal imbalance. A targeted exome revealed a heterozygous c.250T>G p.(Tyr84Asp) substitution in the *SOX9* gene (NM\_000346.3), which was confirmed by Sanger analysis. This variant was not present in either parent. To our knowledge, this substitution

has not yet been described. Its de novo nature and correlation with the patient's phenotype strengthen the probability of its pathogenicity. Moreover, this *SOX9* missense variant involves a nucleotide which has been highly conserved throughout evolution, and the physicochemical properties significantly differ between tyrosine and aspartate residues. Finally, this variant was predicted to most likely be pathogenic according to most simulation programs (DANN pathogenic score 0.99) and is not reported in the Exome Aggregation Consortium (ExAC) database. We came to the conclusion that this variant is pathogenic. Due to the absence of bowed long bones, the diagnosis of ACD was retained.

### 3 | DISCUSSION

Campomelic dysplasia and its clinical variant ACD are caused by *SOX9* haploinsufficiency, predominantly due to de novo heterozygous loss-of-function mutations, and more rarely due to chromosomal rearrangement upstream to or involving *SOX9*. This gene, located at 17q24, belongs to the *SOX* (Sry HMG-box) gene family.<sup>4</sup> The *SOX* genes are critical developmental genes which encode transcription factors.<sup>5</sup> Studies have shown that *SOX9* is not only a crucial regulator of cartilage and genital development, but is also important for the development of the central and peripheral nervous system.<sup>6,7</sup> During embryogenesis, it is expressed in a large number of tissues, including the neural tube and olfactory bulbs.<sup>8</sup> Surprisingly, only two papers have reported the absence of olfactory bulbs and tracts in autopsied CD cases. In 1983, Houston et al<sup>9</sup> reported 17 autopsied cases of CD, approximately half of which showed this feature. Twelve years later, Mansour et al<sup>10</sup> provided the necropsy details for 22 CD patients, with agenesis of the olfactory bulbs observed in 25%. To our knowledge, there have been no recent descriptions of this important sign.

### 4 | CONCLUSION

The clinical severity and high neonatal lethality of CD and ACD emphasize the importance of their accurate prenatal diagnosis. This report illustrates the agenesis of olfactory bulbs in an ACD patient on prenatal and postnatal MRI. As prenatal MRI scans become increasingly available, this particular feature should be looked for to help establish an accurate diagnosis of fetuses presenting signs of skeletal dysplasia. Prospective studies should be conducted to accurately assess the frequency of agenesis of olfactory bulbs related to *SOX9* mutations.

### CONFLICT OF INTEREST

None declared.

### AUTHORS CONTRIBUTIONS

M-JD: involved in patient management, wrote the manuscript and reviewed the manuscript. VB: provided genetic analysis of samples, wrote the manuscript and reviewed the manuscript. MC: provided analysis of prenatal and postnatal MRI images. KG: involved in patient management and provided analysis of prenatal US images. NG: provided analysis of postnatal MRI images. CM: involved in patient management. AR: involved in patient management. IM: involved in patient management, provided genetic analysis of samples, wrote the manuscript and reviewed the manuscript.

### ORCID

Isabelle Maystadt  <https://orcid.org/0000-0001-7170-8186>

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**How to cite this article:** Debuf M-J, Benoit V, Cassart M, et al. Agenesis of olfactory bulbs: A forgotten diagnostic indicator of acampomelic campomelic dysplasia. *Clin Case Rep*. 2019;7:1352–1354. <https://doi.org/10.1002/ccr3.2228>